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Drug Information Service
Department of Pharmacy
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196
www.cc.nih.gov/phar

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor
Karim Anton Calis, Pharm.D., M.P.H.
Clinical Specialist, Endocrinology & Women's Health, and Coordinator, Drug Information Service
kcalis@nih.gov

In This Issue

Drug Interactions: A Guide for Clinicians

Introduction

A *drug interaction* is defined as the pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone (1,2). It should be noted that the term "drug interaction" usually has a negative connotation. While drug interactions may lead to a loss of therapeutic effect or toxicity, they may also benefit the patient. The use of certain drugs in combination can lead to improved outcomes or improve a drug regimen's convenience, reduce costs, or improve the side effect profile. For example, the concomitant use of probenecid and ampicillin has been used for years to achieve high and prolonged concentrations of the antibiotic (3).

In addition to drug-drug interactions, there are a variety of other substances that can alter the pharmacokinetics and/or effect of drugs. These include foods, nutritional supplements, cytokines, formulation excipients, and environmental factors (e.g., cigarette smoke). All of these factors require consideration in the evaluation of a patient with a suspected drug interaction.

The assessment of drug interactions remains an integral component of patient management. This is especially true in elderly patients who often have various chronic diseases for which they receive multiple medications. Patients who receive their care from more than one provider and their medications from more than one pharmacy are also prone to interactions. In addition, drug interactions are common in disease states for which multi-drug therapy is the standard of care, such as tuberculosis, HIV infection, and cancer. It is not uncommon for HIV-infected patients to be receiving 8-10 different medications with each having its own food restrictions, dose-spacing requirements, and complex interaction profile.

In this article, drug interactions will be described on the basis of major mechanisms. *Pharmacokinetic interactions* are those in which the concentrations of one or more drugs may be altered by another. These interactions may occur by changes in absorption, distribution, metabolism, or excretion. However, it is important to note that multiple mechanisms may co-exist. For example, co-administration of quinidine and digoxin leads to increased digoxin levels by reducing the renal and biliary clearance of digoxin, by decreasing its volume of distribution, and perhaps by modulation of transport proteins (4). *Pharmacodynamic interactions* refer to additive, synergistic, or antagonistic effects resulting from co-administration of two or more drugs. The synergistic actions of certain antibiotics have long been a mainstay of therapy against organisms that are difficult to eradicate such as *Pseudomonas aeruginosa* or *Mycobacterium tuberculosis.* Drugs with overlapping toxicities, such as ethanol and benzodiazepines, could lead to more serious adverse effects than when either is agent given alone. An understanding of interaction mechanisms is needed to optimize drug therapy.

Epidemiology

The incidence of drug interactions varies widely in the literature ranging from 2.2–70.3% (5-12). The incidence is increased in the elderly, especially in those patients who are confined to nursing homes. Patients with multiple organ dysfunction and patients receiving polypharmacy are also at an increased risk. Recent data on HIV-infected

patients estimate that drug interactions occur in up to 77% of patients receiving protease inhibitors (13). The clinical consequences of these interactions have not been well

described. One study of hospitalized patients reported that the incidence of symptoms due to a drug interaction was only between 0 and 1% (11). However, many serious drug interactions have been described. In some cases, such as interactions of terfenadine or cisapride with azole antifungals, interactions may result in death (14,15). Mibefridil, terfenadine, astemizole, and cisapride have been removed from the U.S. market in recent years solely because of the life-threatening potential of interactions with these drugs.

Classifications

Drug interactions can be classified based on their severity and on the probability that the interaction exists. Severity is usually classified as minor, moderate, or severe. *Minor drug interactions* usually have limited clinical consequences and require no change in therapy. For example, acetaminophen may reduce the effects of furosemide. However, this interaction is unlikely to cause any clinical effects or warrant a change in dose (16). A *moderate interaction* would be the increased incidence in hepatitis resulting from combined therapy with rifampin and isoniazid. Although the increased toxicity of this combination is clearly known, it would still be used along with frequent monitoring of liver enzymes. A *severe drug interaction* would involve potentially serious toxicity and require a change in dose, drug, or dosing schedule. The classic example of a severe interaction is the life-threatening cardiac arrhythmia that may occur when terfenadine is combined with ketoconazole (14). Severe interactions require the discontinuation of one of the co-administered agents.

The likelihood that an interaction is caused by a drug is usually classified as established, probable, suspected, possible, or unlikely. This is determined by documentation of similar interactions in published clinical and *in vitro* studies, case reports, pre-clinical studies and anecdotes. Interactions may further be classified on the basis of the time course of the interaction. Certain interactions occur immediately with concomitant administration such as the chelation of fluoroquinolone antibiotics and antacids which results in an immediate decrease in fluoroquinolone absorption. Other interactions require several hours or days to develop such as the reduction in the effects of warfarin by co-administration of vitamin K.

Mechanisms of Drug Interactions

Interactions Affecting Drug Absorption

Interactions that affect drug absorption can be dramatic in nature. A number of mechanisms can affect drug absorption including a change in gastric pH, chelation, ion exchange, change in gastric motility, alteration in gut flora, modulation of transport proteins, or inhibition of intestinal enzymes.

Certain drugs, such as ketoconazole and itraconazole, require an acidic gastric pH for optimal dissolution so they can be absorbed in the small intestine. The addition of agents, such as proton pump inhibitors, H_2 receptor antagonists, and antacids, that raise the gastric pH will markedly reduce the absorption and plasma concentrations of these antifungal drugs (17,18). For example, the combination of ranitidine and ketoconazole led to a reduction in the area under the plasma level-vs.-time curve (AUC) of ketoconazole by over 50% (17). Decreases in ketoconazole absorption by pH-raising agents have led to therapeutic failure (19). In these situations, fluconazole can be used as an alternative since its absorption is not pH-dependent (20).

Chelation is the irreversible binding of drugs in the gastrointestinal tract. Tetracyclines have long been reported to bind with antacids, leading to inactivation of these antibiotics (21). Quinolone antibiotics also chelate with di- and tri-valent cations such as the aluminum or magnesium in antacids, calcium in dairy products, and ferrous sulfate in iron replacement agents (22). In general, these interactions reduce the AUC of the quinolone by over 75%. While these interactions are clearly clinically relevant, they are also easy to avoid by administering the antibiotic two hours before the antacid is given. A change in dose or drug is unnecessary. Chelation interactions represent a severe interaction in which a simple change in dose scheduling is all that is required to avoid the loss of antibiotic activity.

A large number of drugs have been reported to interact with the anionic exchange resins such as cholestyramine (23). These exchange resins form insoluble complexes with warfarin, digoxin, beta-blockers, nonsteroidal anti-inflammatory drugs, and other drugs, thereby decreasing their absorption and leading to low plasma concentrations. A separation between doses is again often the only intervention required. However, exchange resins need to be administered frequently during the day and staggered dosing may be very inconvenient for the patient.

Enteric bacteria can metabolize digoxin within the intestine and reduce its bioavailability. Conversely, administration of antibiotics that alter gut flora have been reported to increase digoxin absorption in some patients (24). Antibiotics may also inhibit the growth of gut flora which hydrolyze steroid conjugates. This inhibition decreases enterohepatic recirculation of oral contraceptives and may lower their plasma concentration. Although reports of unplanned pregnancies have been attributed to this interaction, several other clinical studies have found that contraceptive blood concentrations are unchanged by concomitant antibiotic therapy (25,26).

Interactions Affecting Protein Binding

The extent to which protein binding displacement interactions result in clinically significant drug interactions has been largely overstated (27). Very few drug interactions have been identified based on this mechanism, and many that were previously thought to be protein-binding interactions have been identified as being metabolically based interactions. The extent and significance of protein binding displacement interactions is to some extent dependent on whether the displaced drug is restrictively or non-restrictively eliminated.

Restrictively metabolized drugs: For restrictively metabolized drugs, only unbound drug in plasma can be cleared. An increase in the unbound fraction in plasma will result in a proportional increase in total (bound + unbound) drug elimination clearance and a decrease in total drug concentration in plasma. An increase in the unbound concentration of drug in plasma occurs immediately after addition of the displacing drug. However, it will gradually return to pre-displacement concentrations as long as intrinsic clearance remains unchanged (27–29). For most drugs, this transient increase in unbound concentration will not be clinically significant. However, this transient increase may be clinically significant for drugs with a small distribution volume distribution, a long elimination half life, and a narrow therapeutic index. A clinically significant interaction that occurs solely by plasma protein displacement is the displacement of warfarin from serum albumin by a metabolite of chloral hydrate (trichloroacetic acid) which transiently increases the unbound concentration of warfarin (29).

Nonrestrictively metabolized drugs: For nonrestrictively metabolized drugs, elimination clearance is dependent on hepatic blood flow and increases in unbound drug concentrations in plasma will not lead to an increase in clearance. Therefore, in contrast to the situation with restrictively metabolized drugs, an increase in the unbound fraction will lead to an immediate and sustained increase in unbound concentration (27,29). However, no examples of clinically significant plasma protein displacement interactions involving nonrestrictively metabolized drugs have been identified (29,30). Some reasons for the lack of clinically significant interactions are that many nonrestrictively cleared drugs have a relatively wide therapeutic index and the relationships between drug concentration and response are not well defined (30).

Interactions Affecting Drug Metabolism

Most drugs undergo biotransformation via phase I and/or phase II metabolic reactions in the liver. Many phase I reactions, such as dealkylation, deamination and hydroxylation, involve the cytochrome P-450 (CYP450) monooxygenases. Research on CYP450 isoenzymes has grown exponentially in the past decade. Advances in the application of scientific methods to identify the amino acid sequences of specific CYP450 isoenzymes has furthered research in this area as well as the identification of specific genetic polymorphisms for these isoenzymes. Additionally, the ability to fully characterize the CYP450 metabolism of drugs and their interaction with CYP450 isoenzymes, largely through *in vitro* methods using drug probes and cDNA expressed isoenzymes in human liver microsomes, has furthered understanding of this area of drug metabolism.

Phase II conjugation reactions, such as glucuronidation and sulfation, involve the microsomal uridine diphosphate (UDP) glucuronosyltransferases and the cytosolic sulfotransferases, respectively. Although drug interactions involving phase II enzymes can occur, much less research has been completed in this area. Therefore, this article will focus on drug metabolism interactions involving the CYP450 enzyme system. Thus far 14 families of CYP450 enzymes common to all mammals have been identified (31). However, only 3 of these families (CYP1, CYP2, and CYP3) are thought to be important in the metabolism of drugs. Isoenzymes within these families that have been identified as important in drug metabolism include CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Of these isoenzymes, CYP3A4 is the most abundant, comprising 25% of total hepatic CYP450 (32). This isoenzyme is responsible for the metabolism of a vast array of structurally diverse drugs and, coupled with its expression in gut wall, may be responsible for the metabolism of the majority of xenobiotics.

Table 1 lists drugs as substrates, inhibitors, and/or inducers of various isoenzymes. Although this table can be used as a basic guide to predict drug-drug interactions involving CYP450 isoenzymes, many variables are not included which would assist in interpreting the clinical significance of these interactions, e.g., potency of inhibition. In simplistic terms, a drug that is a substrate for an isoenzyme may be considered an inhibitor of that isoenzyme, although the potency of the inhibition will depend on many factors. However, the converse is not necessarily true. Quinidine, for example, is the most potent inhibitor thus far identified for CYP2D6 but it is metabolized by CYP3A4 (33).

Until recently, the pathways of drug metabolism and the inhibiting or inducing effects of drugs on various CYP450 isoenzymes were not fully determined. However, a new emphasis on characterizing the metabolism of drugs and their effects on CYP450 isoenzymes occurred secondary to identification of the potentially fatal metabolic drug interaction between terfenadine, a prodrug that is metabolized by CYP3A4 to an active metabolite, and ketoconazole and macrolide antibiotics that inhibit the activity of CYP3A4 (14,34). Due to the life-threatening risk of *torsades de pointes* when terfenadine is used with CYP3A4 inhibiting drugs and the non-life-threatening indications for which these drugs were developed, it was deemed that the risk benefit ratio did not merit its continued availability. Therefore, this drug is no longer marketed in the United States.

As a result of this experience, the Food and Drug Administration now requires characterization of the metabolic pathways of a new drug and its inducing and inhibiting effect on specific isoenzymes (35). In addition, pharmaceutical companies are beginning to base product development decisions on the information generated from these studies. For example, knowledge of the drug interaction involving terfenadine led to the development of the active metabolite, fexofenadine, which is a nonsedating antihistamine without QT-interval prolonging effects. Norastemizole and (+) norcisapride also are being evaluated as improved chemical entities which are thought not to have the QT-inteval prolonging properties of their respective parent compounds (36). However, the overall benefit of a specific drug is another factor which must be

Table 1. Selected CYP450 Substrates, Inhibitors and Inducers

	CYP1A2	CYP2B6	CYP2C9 (polymorphic)	CYP2C19 (polymorphic)	CYP2D6 (polymorphic)	CYP2E1	CYP3A4		
SUBSTRATES	Amitriptyline	Amitriptyline	Amitriptyline	Amitriptyline	Bufuralol	Acetaminophen	Alfentanyl	Erythromycin	Progesterone
	Caffeine	Bupropion	Celecoxib	Citalopram	Codeine	Chlorzoxazone	Alprazolam	Estradiol	Quetiapine
	Clomipramine	Cyclophosphamide	Fluoxetine	Clomipramine	Desipramine	Enflurane	Astemizole	Felodipine	Quinidine
	Clozapine	Lidocaine	Fluvastatin	Cyclophosphamide	Dexfenfluramine	Ethanol	Atorvastatin	Fentanyl	Quinine
	Cyclobenzaprine	Midazolam	Diclofenac	Imipramine	Dextromethorphan	Halothane	Buspirone	Finasteride	Ritonavir
	Estradiol	Nevirapine	Fluoxetine	Indomethacin	Donepezil	Isoflurane	Caffeine	Haloperidol	Salmeterol
	Fluvoxamine	Procainamide	Glipizide	Lansoprazole	Encainide	Methoxyflurane	Carbamazepine	Hydrocortisone	Sildenafil
	Imipramine	Promethazine	Ibuprofen	Nelfinavir	Fluvoxamine	Sevoflurane	Cerivastatin	Indinavir	Simvastatin
	Melatonin	Tamoxifen	Irbesartan	Nilutamide	Haloperidol	Theophylline	Chlorpheniramine	Lidocaine	Tacrolimus
	Mexiletine	Temazepam	Losartan	Omeprazole–	Lidocaine		Cisapride*	Loratadine	Tamoxifen
	Olanzapine	Testosterone	Phenytoin	Pantoprazole	Mexiletine		Citalopram	Lovastatin	Taxol
	Propranolol	Valproic acid	Piroxicam	Phenytoin	Nortiptyline		Clarithromycin	Methadone	Testosterone
	Riluzole	Verapamil	Sertraline	Progesterone	Ondansetron		Clozapine	Midazolam	Terfenadine*
	Ropivacaine		Sulfamethoxazole	Propranolol	Propranolol		Codeine	Nefazodone	Trazodone
	Tacrine		Suprofen	Teniposide	Risperidone		Cyclosporine	Nelfinavir	Triazolam
	Theophylline		Tamoxifen	R-warfarin	Sertraline		Dapsone	Nifedipine	Verapamil
	Verapamil		Tolbutamide		Tamoxifen		Donepezil	Nisoldipine	Vincristine
	R-warfarin		Torsemide		Thioridazine		Dextromethorphan	Nitrendipine	Zaleplon
	Zileuton		S-warfarin		Tramadol		Diazepam	Ondansetron	Zolpidem
	Zolmitriptan				Venlafaxine		Diltiazem	Pimozide	
INHIBITORS	Amiodarone	Amiodarone	Amiodarone	Cimetidine	Amiodarone	Disulfiram	Amiodarone	Fluoxetine	Nefazodone
	Ciprofloxacin	Ketoconazole	Fluconazole	Felbamate	Celecoxib		Cimetidine	Fluvoxamine	Nelfinavir
	Enoxacin	Orphenadrine	Fluoxetine	Fluoxetine	Chlorpheniramine		Ciprofloxacin	Gestodene	Norfloxacin
	Fluvoxamine	Tranylcypromine	Fluvastatin	Fluvoxamine	Cimetidine		Clarithromycin	Grapefruit juice	Mibefradil*
	Furafylline	Troglitazone	Fluvoxamine	Indomethacin	Clomipramine		Delaviridine	Indinavir	Ritonavir
	Methoxsalen	Troleandomycin	Isoniazid	Ketoconazole	Fluoxetine		Diltiazem	Itraconazole	Saquinavir
	Mibefradil*		Lovastatin	Lansoprazole	Methadone		Erythromycin	Ketoconazole	Troleando-
	Norfloxacin		Paroxetine	Modafinil	Mibefradil*		Fluconazole	Mifepristone	mycin
	Ticlopidine		Phenylbutazone	Omeprazole	Paroxetine				
			Sertraline	Oxcarbazepine	Quinidine				
			Teniposide	Paroxetine	Ritonavir				
			Zafirlukast	Ticlopidine	Terbinafine				
				Topiramate					
INDUCERS	Cruciferous	Dexamethasone	Rifampin	Norethindrone	None identified	Ethanol	Barbiturates	Oxcarbazepine	
	vegetables	Phenobarbital	Secobarbital	Prednisone		Isoniazid	Carbamazepine	Phenobarbital	
	Char-grilled meat	Rifampin		Rifampin			Efavirenz	Phenytoin	
	Insulin	Sodium valproate					Glucocorticoids	Rifampin	
	Omeprazole						Modafinil	St. John's wort	
	Tobacco						Nevirapine	Troglitazone	

* Withdrawn from U.S. market

considered in making risk/benefit decisions. For example, the protease inhibitors are potent inhibitors of CYP3A4 but, in the absence of other more effective therapies, their utility in treating HIV warrants their continued availability. Conversely, the calcium channel blocker mibefradil was withdrawn from marketing because of its potent CYP3A4 inhibitory effects and availability of equally effective therapeutic alternatives.

Inhibition of CYP450 enzymes: Inhibition can be characterized as reversible, quasi-irreversible, and irreversible (32,37). The type of inhibition most commonly involved in drug interactions is reversible upon discontinuation of the inhibitor, and isoenzyme function is regained generally over one elimination half-life of the inhibitor. Distinguishing between quasi-irreversible and irreversible inhibition from a clinical standpoint is less important since the differentiation is the reversibility of the inhibition in an *in vitro* environment. The mechanism of both of these irreversible inhibitions involves formation of a stable complex with the inhibitor and the prosthetic heme group of CYP450 such that the CYP450 is sequestered in a functionally inactive state. Enzyme activity can only be restored by generating new CYP450. Examples of noncompetitive inhibitors that form complexes with CYP450 enzymes include the macrolide antibiotics, erythromycin and troleandomycin.

Reversible inhibition can be described as having a competitive, noncompetitive, or uncompetitive mechanism. *Competitive inhibition*, the most common type implicated in drug-drug interactions, occurs when the inhibitor binds to the active site of the free enzyme thus preventing substrate binding. The onset and time course of competitive

inhibition follow the half-life and time to steady-state of the inhibitor drug. The time to maximal drug interaction will also depend on the time required for the substrate to reach a new steady state. For *noncompetitive inhibition*, substrate binds to one site on the enzyme while the inhibitor binds to another site, thereby making the enzyme-substrate-inhibitor complex nonfunctional. *Uncompetitive inhibition* occurs when the inhibitor binds to the enzyme-substrate complex rendering it nonfunctional.

While inhibition of CYP450 enzymes leads to increased concentrations of the substrate drug, the following questions need to be considered in order to assess the clinical relevance of these interactions.

1. *What is the toxic potential and therapeutic index of the substrate?* When evaluating the clinical relevance of a drug interaction, it is important to consider the therapeutic index of the substrate drug. For example, inhibition of terfenadine metabolism may result in QT prolongation and *torsades de pointes* while inhibition of sertraline metabolism is not associated with such serious cardiovascular sequelae. However, it should be kept in mind that inhibition of sertraline metabolism could lead to an increased incidence of other side effects.
2. *What are the other pathways involved in the metabolism of the substrate?* If the substrate drug is metabolized by multiple CYP450 pathways and is combined with an inhibitor which is specific for one pathway, the drug will be less affected than if it is only metabolized by the inhibited pathway. For example, *in vitro* studies have estimated that zolpidem is metabolized by CYP3A4 (61%), CYP2C9 (22%), CYP1A2 (14%), CYP2D6 (< 3%), and CYP2C19 (< 3%), whereas triazolam is almost exclusively metabolized by CYP3A (38,39). Addition of ketoconazole to zolpidem will increase zolpidem AUC by 67% compared to a 1,200% increase in triazolam AUC (40,41).
3. *What is the role of active metabolites of the substrate?* If active metabolites are required for therapeutic efficacy, an inhibitor may decrease formation of the metabolites with resultant loss of therapeutic efficacy. For example, codeine is metabolized to its active analgesic metabolite, morphine, via CYP2D6. Inhibition of this isoenzyme is likely to reduce the analgesic effect of codeine and codeine-derivatives (42).
4. *What are the consequences of metabolic inhibition of metabolites*? For many metabolites, especially ones which are devoid of desired pharmacologic effects, the metabolic pathways may not be well understood. However, one should be aware of possible clinical consequences of this type of inhibition. For example, nefazodone is a CYP3A4 substrate while one of its main metabolites, meta-chlorophenylpiperazine (mCPP) is a substrate of CYP2D6. Inhibition of CYP2D6 will result in increases in mCPP concentration and side effects such as anxiety (43).
5. *Does the inhibitor inhibit multiple CYP450 isoenzymes?* One should consider if the inhibitor inhibits multiple CYP450 isoenzymes. Drugs which inhibit multiple pathways will be more likely to inhibit the metabolism of drugs which are metabolized by multiple pathways. For example, cimetidine is a well-known inhibitor of multiple CYP450 isoenzymes.
6. *Is the patient a poor metabolizer of an isoenzyme for which the inhibitor is specific?* At the current time, patients are not generally genotyped or phenotyped for polymorphic CYP450 isoenzymes (CYP2C9, CYP2C19, and CYP2D6). However, if a patient is a poor metabolizer of a specific isoenzyme, addition of an inhibitor will not affect the metabolism of the substrate drug because the isoenzyme already contributes relatively little to that drug's metabolism. For example, a CYP2D6 poor metabolizer receiving desipramine (a CYP2D6 substrate) would not be expected to exhibit elevated desipramine concentrations with co-administration of a specific CYP2D6 inhibitor (42,44). However, the dose of desipramine administered to this individual would be lower than a normal dose due to the absence of functional CYP2D6 and the lack of full metabolic compensation by other CYP isoenzymes.
7. *Do otherwise pharmacologically inert metabolites of the inhibitor inhibit CYP450 isoenzymes?* In most cases, this information will not be known. However, otherwise inert drug metabolites can affect the activity of CYP450 isoenzymes. Paroxetine is a well-documented potent CYP2D6 inhibitor, and it appears that one of its glucuronidated metabolites (M-II) also contributes to this inhibition (45).
8. *Is the inhibition potentially harmful or helpful?* Although one usually considers inhibition of drug metabolism as potentially harmful, these interactions can be exploited to enhance therapeutic effect. Combinations of ketoconazole and cyclosporine have been used as a way to save drug costs and doses of this expensive immunosuppressant (46). Ritonavir, an inhibitor of CYP3A4, also increase the bioavailability of saquinavir by 20-fold, allowing for a reduced saquinavir dosage and a lower pill burden (47).

Induction of CYP450: The net effect of induction is increased DNA transcription and synthesis of CYP450 enzymes. With the exception of CYP2D6, all of the CYP450 isoenzymes are inducible. The time course of induction depends on the elimination half-life of the inducer as well as the time required for enzyme degradation and new enzyme production (48). As with CYP450 inhibition, there are multiple clinical consequences of CYP450 induction. Addition of an inducer will decrease the substrate concentration and therapeutic failure may result. Similarly, discontinuation of an inducer will increase the substrate concentration in a time-dependent fashion, and toxicity may result. CYP450 inducers may also accelerate formation of reactive metabolites which may be harmful. For example, alcohol induces CYP2E1 with a resultant increase in formation of acetaminophen toxic metabolites, thus predispose patients to hepatotoxicity. At the current time, at least five mechanisms of enzyme induction have

been identified: induction by the aryl hydrocarbon receptor, ethanol, peroxisome proliferators, the constitutive androstane receptor (CAR), and the pregnane X receptor (PXR) (49). Two additional nuclear receptors, liver X receptors and farnesoid X receptors, may also be involved in enzyme induction (48,50).

The CAR and PXR orphan nuclear receptors are primarily affected by drugs and, similar to CYP3A4 and P-gp, there appears to be considerable overlap of drugs affecting these receptors (48). Induction involving PXR is most pronounced on CYP3A4, while induction involving the CAR receptor is most pronounced on CYP2B6. The orphan nuclear receptor, CAR, appears to be the target of phenobarbital-type induction (48). Data regarding specific isoenzymes linked to CAR-mediated induction come largely from drug interaction studies with phenobarbital-type inducers. The most pronounced inductive effect involves CYP2B6 with some effects also noted for CYP2C9, CYP3A4, CYP1A2, and some UDP-glucuronosyltransferases. Induction involving PXR was formerly termed rifampicin/glucocorticoid-type induction. It has recently been determined that the human PXR binds to the rifampicin/dexamethasone response element in the CYP3A4 promotor region as a heterodimer with the 9-cis-retinoic acid receptor (RXR). The hPXR/RXR complex is activated by a number of drugs, including rifampin, dexamethasone, phenobarbital, clotrimazole, and spironolactone, which have been shown to modulate *CYP3A4* expression. Additionally, the CYP3A4 inducing herbal preparation, St. John's wort, has been shown to activate the PXR (50). The identification of this receptor is important in that PXR binding and activation assays can be used to predict which compounds are likely to induce CYP3A4 rather than relying on *in vitro* assay methodology using human liver slices.

Induction of P-glycoprotein and intestinal CYP450: CYP450 is expressed in large concentrations on the intestinal epithelium and can be involved in presystemic drug metabolism. Levels of CYP450 in the gut wall are generally 20–50% of those in the liver but there is considerable variability (52). Substances that inhibit gastrointestinal CYP3A4 can markedly increase the bioavailability of CYP3A4 substrates. The enterocytes in the intestinal mucosa are also a site of expression of transporter proteins that also play a critical role in drug metabolism and disposition. Many drug transporters have thus far been identified including organic anion-transporting polypeptide (OATP), organic cation transporters (OCTs) and P-glycoprotein (P-gp). Although all of these transporters are likely important in drug metabolism, P-gp has been the most studied of the drug transporters.

P-gp is the product of the human multidrug resistance gene (*mdr1*) that has been recognized as a contributor to resistance for a variety of chemotherapeutic agents by decreasing the intracellular accumulation of anticancer drugs (53). P-gp is an efflux transporter present in the gastrointestinal epithelium, liver, kidney, and endothelial cells making up the blood-brain barrier. This transporter is thought to be important in the absorption, distribution, and elimination of many drugs. P-gp restricts drug entry into and through the intestinal epithelium by transporting drugs back into the intestinal lumen, thereby decreasing drug bioavailability. Because P-gp transports drugs back into the lumen, it may also increase their exposure time to CYP3A4 present in the gut wall. Thus intestinal expression of CYP3A4 and P-gp may serve complementary roles in limiting drug absorption.

In addition to tissue distribution, there appears to be a significant overlap with regard to CYP3A4 substrates and inhibitors and P-gp substrates and inhibitors (Table 2). This overlap obscures the specific contribution of inhibition of CYP3A4 and modulation of P-gp function to gastrointestinal site interactions. One exception is the P-gp substrate digoxin, a metabolite of the CYP3A4 substrate digitoxin, but not itself a substrate of this isoenzyme. However, not all drugs listed as CYP3A4 substrates or inhibitors have been evaluated with regard to their role as substrates or inhibitors of P-gp. In addition, drugs which inhibit both CYP3A4 and P-gp may have very different inhibitory potencies, i.e., a drug may be more selective for P-gp inhibition compared to CYP3A4 inhibition (54).

Some substances, such as grapefruit juice, affect CYP3A4 only in the gut wall and not the liver. Grapefruit juice contains various flavinoids that have been well documented to be inhibitors of gastrointestinal CYP3A4. Large increases in bioavailability have been reported when grapefruit juice has been administered concomitantly with drugs that have extensive intestinal wall metabolism (55,56). For example, saquinavir exposure increases by 50–200% when co-administered with grapefruit juice (57). Other drugs noted to have increased bioavailability with grapefruit juice include beta-blockers, calcium channel blockers, benzodiazepines, and HMG CoA-reductase inhibitors (55).

Grapefruit juice also appears to have inhibitory effects on P-gp-mediated enterocyte transport. For example, P-gp may mediate the large increase in cyclosporine bioavailability that occurs when this drug is co-administered with grapefruit juice. However, P-gp and CYP3A4 may have opposing effects. Co-administration of the protease inhibitor indinavir and grapefruit juice leads to either a decrease in indinavir levels or no effect, suggesting that activation of P-gp may negate any increased bioavailability from CYP3A4 inhibition (57,58). Regardless, inhibition of CY3A4 or modulation of P-gp in the gut wall can have a major impact on drug absorption and drug interactions. Since grapefruit juice is a natural product, there is wide variability which makes these interactions very unpredictable in individual patients. The severity of the interaction may depend on how much and how often the grapefruit juice was consumed, the timing of the grapefruit juice and the medication dose, the specific brand of juice, and whether it was double or single strength.

The use of P-gp inhibitors to increase intracellular concentrations of chemotherapeutic agents in tumor cells is being evaluated in patients with multi-drug resistant tumors. Such compounds also may be very useful to target

Table 2. P-glycoprotein Substrates and Inhibitors

Substrates		Inhibitors	
Amiodarone	Mefloquine	Actinomycin	Mitomycin C
Bepridil	Nicardipine	Amprenavir	Mitoxantrone
Cefoperazone	Nifedipine	Celiprolol	Morphine
Ceftriaxone	Nitrendipine	Colchicine	Nelfinavir
Clarithromycin	Progesterone	Cortisol	Nicardipine
Cortisol	Propranolol	Cyclosporine	Nifedipine
Cyclosporine	Quercetin	Daunorubicin	Paclitaxel
Diltiazem	Quinine	Dexamethasone	Progesterone
Dipyridamole	Quinidine	Digoxin	Rifampin
Erythromycin	Reserpine	Diltiazem	Ritonavir
Itraconazole	Tacrolimus	Docetaxel	Saquinavir
Felodipine	Tamoxifen	Doxorubicin	Tacrolimus
Fluphenazine	Terfenadine*	Erythromycin	Taxol
Hydrocortisone	Testosterone	Etoposide	Teniposide
Ketoconazole	Trifluoperazine	Fexofenadine	Terfenadine*
Lidocaine	Verapamil	Hydrocortisone	Topotecan
Indinavir	Vincristine	Ivermectin	Vinblastine
Loperamide			

* Withdrawn from U.S. market

drug delivery to the central nervous system. Studies in knockout mice have suggested that P-gp inhibition may result in higher cerebrospinal fluid concentrations of P-gp substrates (59). Ketoconazole, an inhibitor of both CYP3A4 and P-gp, was shown to cause a larger increase in CSF levels of saquinavir and ritonavir relative to unbound plasma levels (60). Unfortunately, potent P-gp inhibitors often have limited utility since they have pharmacologic effects that set dose limits below those needed for P-gp inhibition. Currently, specific P-gp inhibitors are being developed that lack undesired pharmacologic effects. However, the strategy of administering a P-gp inhibitor to increase drug exposures must be considered in light of the consequences of inhibiting a protein with wide distribution in the body. General inhibition of P-gp function in various tissues may be met with significant central nervous system and other adverse effects.

Prediction and Clinical Management of Drug Interactions

In vitro Screening Methods

It is impossible to study in patients every possible combination of drugs that may be used clinically. Although nonhuman mammalian species are often used for *in vivo* screens for drug interactions, well documented differences in enzyme expression and regulation between these species and humans weakens clinical extrapolation of these results. For these reasons, a variety of *in vitro* systems are being relied upon to screen for and assess CYP450-mediated drug interactions (61). Microsomes, hepatocytes, liver slices, purified P450 enzymes, and recombinant human P450 enzymes have all been used to assess if a drug candidate will affect concomitantly administered agents. For new drug development, the ability to predict *in vivo* drug interactions from *in vitro* studies has become a useful tool in the decision to develop a drug candidate (62). *In vitro* methods have been shown to predict *in vivo* interactions with some drugs such as paclitaxel (63).

While these *in vitro* systems can certainly be useful, numerous limitations and caveats warrant consideration. In general, many systems can only evaluate enzyme inhibition, and are not useful to assess induction. Also, *in vitro* results cannot necessarily be extrapolated to clinical studies for drugs with multiple metabolic pathways. *In vitro* studies predicted that methadone concentrations would be markedly increased by concomitant use of ritonavir (64). However, a study in healthy volunteers demonstrated that methadone concentrations actually decreased (65). These discordant results were due to a variety of factors not evaluable *in vitro*, including protein binding, disposition of isomers, and involvement of multiple CYP isoenzymes. Additionally, it is important that concentrations of inhibitors are used for *in vitro* testing that are not several fold higher than expected *in vivo*. Finally, all *in vitro* screening studies should include positive controls for inhibition (e.g., ketoconazole for CYP3A4, quinidine for CYP2D6) and induction (e.g., rifampin for CYP3A4).

Predicting Drug Interactions in Individual Patients

An understanding of basic interaction mechanisms is essential to identifying and managing drug interactions. Interactions involving drug metabolism are of greatest clinical significance and a working knowledge of the major classes of drugs that affect CYP450 metabolism combined with a review of medication profiles can prevent serious interactions from occurring. However, a variety of additional factors may be responsible for the occurrence and severity of an interaction in an individual patient. Genetics, environmental factors (e.g., cigarette smoke), foods, concomitant diseases, impaired organ function, and age may all play a role in determining if an interaction will occur and what clinical effects will result. These factors make it difficult to predict the magnitude or clinical significance of a drug interaction for an individual patient.

It is possible to genotype individuals to identify mutant genes that cause patients to be poor metabolizers or extensive metabolizers of some drugs. Although this approach has been shown to predict interactions *in vivo*, genotyping can be affected by various environmental or physiologic factors. A more reliable approach involves phenotyping patients using various probe drugs for specific CYP450 isoenzymes (44). After patients receive a probe drug which is almost exclusively metabolized by one CYP450 isoenzyme, the effect of a putative inhibitor or inducer can be evaluated by examining the formation of metabolites formed from the probe drug in the presence of the inhibitor or inducer. Some examples of probe drugs include caffeine (CYP1A2), tolbutamide (CYP2C9), S-mephenytoin (CYP2C19), chlorzoxazone (CYP2E1), debrisoquine (CYP2D6), sparteine (CYP2D6), dextromethorphan (CYP2D6), erythromycin (CYP3A4), and midazolam (CYP3A4). "Cocktails" of probe drugs can be given in combination to evaluate various metabolic pathways simultaneously.

After administration of a probe drug, urine or blood is collected for a period of time and the ratio of a metabolite and the parent drugs is calculated. These ratios serve as a

biomarker of enzyme activity. For drug interaction studies, these tests can be especially useful when performed prior to, and then after administration of a suspected interacting drug. For example, if an investigator wanted to evaluate the effect of fluoxetine on the CYP2D6 pathway, subjects might be given a dose of dextromethorphan. Urine would be collected and the ratio of metabolite (dextrorphan) to parent drug would be measured. Subjects would then receive either a single dose or steady-state dosing of fluoxetine, after which the dextromethorphan phenotyping study would be repeated. The dextromethorphan/dextrorphan ratios before and after fluoxetine would be compared to assess the effect of fluoxetine on CYP2D6 (66). Phenotyping is not widely used in clinical practice due to the need for extensive analytical capability and expert interpretation, and the invasiveness and expense of the procedures. Despite these limitations, phenotyping remains a useful research tool for characterizing the inhibiting or inducing effects of a drug on a specific isoenzyme.

Clinical Approach to Drug Interactions

Some general principles for recognizing and managing drug interactions follow:

1. At each outpatient visit or hospital admission, a thorough drug history should be recorded that includes over-the-counter medications, investigational drugs and alternative therapies.
2. Because patients may often seek treatment from more than one provider, they should be advised to have all of their medications dispensed at one pharmacy.
3. Maintain a high index of suspicion for a drug interaction when assessing cases of exaggerated toxicity or treatment failure. Consider concomitant diseases and toxicities of current drugs in the patient's regimen, and use a clinical approach for diagnosing adverse drug reactions.
4. If warranted by the clinical circumstances, select drugs with fewer potential interactions. For example, azithromycin is not metabolized by CYP450 and does not possess the interactions associated with other macrolide antibiotics. Similarly, low doses of fluconazole are associated with fewer drug interactions than ketoconazole or itraconazole.
5. Drugs that can be administered once or twice daily may reduce food-related interactions or dosing separation problems.
6. Patient counseling is especially important when proper separation of drug doses is necessary to avoid an interaction (e.g., didanosine and indinavir).
7. The successful management of drug interactions often requires only minimal modifications in dosage or dose scheduling. In some cases, blood level monitoring is available and changes in drug dosing can be guided by pharmacokinetic principles.
8. In some instances pharmacokinetic interactions may be used to simplify complex regimens and reduce pill burden.

Drug interactions remain a major cause of patient morbidity, but can also be used to optimize patient care. The ever increasing numbers of new agents in development will only make management of medication regimens more complex. An understanding of the basic concepts and mechanisms of drug interactions will be a valuable tool in designing safe and effective multi-drug regimens.

References available upon request.

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